ORIGINAL ARTICLE

Use of β_2 agonists in sport: are the present criteria right?

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Background: The regulations for doping control prohibit the use of β_2 agonist bronchodilators (salbutamol, salmeterol, formoterol, and terbutaline) unless the subject follows the procedure known as abbreviated therapeutic use exemption (ATUE).
Objective: To highlight how the interest in discovering possible cheats may result in damage to athletes who really need bronchodilator treatment.
Methods: Thirty one high level athletes (18 men and 13 women) with a previous diagnosis of asthma were examined in our laboratory in order to obtain an ATUE for β_2 agonists. All the subjects underwent spirometry at rest. If the results were normal, the subjects underwent an effort test and, if negative, a methacholine test inhaling progressive doses of methacholine until a fall of 20% in forced expiratory volume in one second (FEV_1) was achieved. The international anti-doping regulations require that the fall in FEV_1 occurs with a concentration of methacholine (PC20) lower than 2 mg/ml (4 mg/ml for Torino 2006). In clinical practice, a test is positive if the response occurs with a PC20 lower than 8 mg/ml.
Results: Only one subject met the criterion for the bronchodilation test at rest. The remaining 30 athletes underwent an effort test, which was positive in nine of them. In 21 cases (13 men and 8 women) the effort test was negative so a methacholine test was carried out. Seven (33%) were negative for ATUE with a PC20 higher than 8 mg/ml, seven (33%) were positive for ATUE with a PC20 less than 2 mg/ml, in four (19%) the PC20 was 2–4 mg/ml, and in three (14%) it was 4–8 mg/ml.
Conclusions: Strict vigilance of fair play should be pursued, but excessive control can lead to situations of inequality for asthmatic athletes such that a third of athletes cannot be treated with β_2 agonists. Therefore under current regulations, asthmatic athletes are often denied the most effective therapeutic option.

The regulations for doping control in most international organisations (International Olympic Committee (IOC), World Anti-Doping Agency (WADA)) and federations (International Association of Athletics Federations (IAAF), International Basketball Federation (FIBA), etc) prohibit the use of β_2 agonist bronchodilators (salbutamol, salmeterol, formoterol, and terbutaline), as well as inhaled corticoids, unless the subject follows the procedure known as therapeutic use exemption or abbreviated therapeutic use exemption (ATUE).[1–3]

It was the IOC Medical Commission (IOC-MC) that established criteria for accepting the use of inhaled β_2 agonists late in 2001 for the Salt Lake City Winter Olympic Games. Owing to the success of its application,[4] these criteria were renewed in January 2004 for the Athens Summer Olympic Games and, more recently, in September 2005, for the Torino 2006 Winter Olympic Games. These criteria require proof of the existence of bronchial hyper-responsiveness at rest (with a bronchodilation test) or after a provocation test with effort, eucapnic voluntary hyperpnoea, inhalation of a hypertonic aerosol, or a methacholine test.[5]

Although objective measures of airway function (for the IOC-MC criteria) may be useful to prevent the non-indicated use of asthma drugs,[6] it is necessary to be careful in establishing such an indication as there are differences from clinical criteria for the general population. These differences affect the bronchodilation test and methacholine test.

The aim of this study is to highlight how the interest in discovering possible cheats may result in damage to athletes who really need bronchodilator treatment.

MATERIALS AND METHODS

Between April 2004 and April 2005, 31 high level athletes (18 men and 13 women) with a previous diagnosis of asthma were examined in our laboratory in order to obtain an ATUE for β_2 agonists. For the men, the mean (SD) age was 23.78 (7.10) years, weight 72.27 (6.61) kg, and height 177.87 (6.53) cm. For the women, the mean (SD) age was 20.69 (7.28) years, weight 63.66 (8.33) kg, and height 168.42 (7.41) cm. Various sports were represented: canoeing (n = 5), athletics (n = 5), swimming (n = 7), rowing (n = 3), sailing (n = 2), triathlon (n = 6), cycling (n = 2), and weightlifting (n = 1).

We focused our attention on the analysis of the bronchodilation test at rest and the methacholine test because they are the ones that may have differences from general practice. All the subjects underwent spirometry at rest. For the bronchodilation test, a forced expiratory volume in one second (FEV_1) of less than 70% of the reference value was required. In this case, after the administration of two inhaled doses of salbutamol, the spirometry was repeated in the following 30 minutes. A positive test was considered to be an improvement in FEV_1 of over 15%, although the new regulations for Torino 2006 require only a 12% improvement.[2]

If the results of spirometry at rest were normal (or the bronchodilation test was negative), an effort test was carried out, with the expectation of an increase of 10% in FEV_1. If this test was negative, the subjects underwent a methacholine test, inhaling progressively larger doses of methacholine (Provocholine). The inhalation started with saline solution followed by increasing concentrations of methacholine (0.025, 0.25, 2.5, 5, 10, and 25 mg/ml) until a fall of 20% in

Abbreviations: ATUE, abbreviated therapeutic use exemption; FEV_1, forced expiratory volume in one second; FEV_1%, FEV_1 as a percentage of forced vital capacity; PC20, concentration of methacholine that produces a fall of 20% in FEV_1; PD20, accumulated dose of methacholine that produces a fall of 20% in FEV_1

Table 1 Results of the methacholine test for the male athletes (n = 13)

Sport	PC20 (mg/ml)	PD20 (IU)
Swimming	1.24	6.87
Athletics	0.02	0.09
Swimming	0.1	1.08
Swimming	0.14	0.78
Rowing	2.88	17.65
Triathlon	3.52	24.08
Triathlon	3.67	25.63
Cycling	6.96	38.67
Swimming	6.38	52.68
Athletics	Negative	
Athletics	Negative	
Athletics	Negative	
Sailing	Negative	

PC20, Concentration of methacholine that produces a fall of 20% in forced expiratory volume in one second; PD20, accumulated dose that produces a fall of 20% in forced expiratory volume in one second.

FEV_1 was achieved. These inhalations were performed using an ultrasonic nebuliser (Hico-Ultrasonat 806E) according to the regulations and recommendations of the Spanish Society of Pneumology and Thoracic Surgery.[7]

For a test to be considered positive, the international anti-doping regulations require that the fall of 20% in FEV_1 occurs with a concentration of methacholine (PC20) lower than 2 mg/ml or an accumulated dose (PD20) lower than 20 IU. The new regulations for Torino 2006 accept a PC20 lower than 4 mg/ml.[2]

All the subjects in this study had a previous diagnosis of asthma made by either a pneumology or allergy service. Following the recommendations to provide the optimal circumstances, the subjects were taken off some drugs before the test: short acting bronchodilators, sodium cromoglycate, nedocromil sodium, and ipatropium bromide for eight hours; long acting bronchodilators, inhaled steroids, and antihistamines for 48 hours; leukotriene antagonists for four days. All the subjects gave written and informed consent. The study was approved by the ethics committee of the Andalusian Center for Sports Medicine.

RESULTS

Only one woman met the criterion for the bronchodilation test at rest, with a FEV_1 of 68% respect to the reference value. After she had inhaled two doses of salbutamol, the FEV_1 improved by 16%. However, in eight cases (26%), the forced vital capacity and FEV_1 (as a percentage of the reference values) were normal, but the FEV_1% value (less than 70%) indicated airflow limitation.

Table 2 Results of the methacholine test for the female athletes (n = 8)

Sport	PC20 (mg/ml)	PD20 (IU)
Swimming	0.02	0.08
Swimming	0.01	0.06
Swimming	0.08	0.43
Canoeing	3.93	28.23
Rowing	6.54	54.33
Canoeing	Negative	
Rowing	Negative	
Canoeing	Negative	

PC20, Concentration of methacholine that produces a fall of 20% in forced expiratory volume in one second; PD20, accumulated dose that produces a fall of 20% in forced expiratory volume in one second.

Table 3 Spirometry values at rest of one of the subjects

	Reference	Actual	%
FVC	5.97	7.95	133
FEV_1	4.97	4.77	95
FEV_1%	–	60%	–

FVC, Forced vital capacity; FEV_1, forced expiratory volume in one second; FEV_1%, FEV_1 as a percentage of FVC.

The remaining 30 athletes underwent an effort test, which was positive in nine of them. In 21 cases (13 men and 8 women), the effort test was negative so a methacholine test was carried out. Of the 21 methacholine tests (tables 1 and 2), seven (33%) were negative for ATUE with a PC20 higher than 8 mg/ml, seven (33%) were positive for therapeutic use exemption with a PC20 less than 2 mg/ml, four (19%) had a PC20 of 2–4 mg/ml, and three (14%) had a PC20 of 4–8 mg/ml.

DISCUSSION

The first problem noted is that the criteria required for the diagnosis of airway hyper-responsiveness are more restrictive for athletes than for patients at large. Thus, in clinical practice, the main criterion for assessing an airflow obstruction in rest spirometry is a reduction in FEV_1%[8–10] such that an index under 70% is an indication for a bronchodilation test by administering a β_2 agonist.

However, such a possibility does not exist for athletes as the only criterion for a bronchodilation test is a fall in FEV_1. The spirometric values for athletes are very often as much as 120% above those for the general population. However, if their FEV_1 is assessed in relation to their own forced vital capacity (which is what FEV_1% measures), an airways obstruction may become evident.[11] Table 3 shows an example of this situation. It gives spirometry results for a 19 year old rower (weight 82 kg, height 188 cm), and we can see that the FEV_1 has a normal value (95% of the reference), but the FEV_1% is lower than 70%. This indicates airflow limitation.[10]

We observed this situation in eight athletes, and this is an ethical dilemma for us: to carry out a provocation test (in order to formalise the ATUE) knowing full well that there is an airflow obstruction, or to rule out the test which prevents the use of drugs that represent the basis of treatment under any guidelines.[12]

The next problem is in the methacholine test. According to the recommendations of the Spanish Society of Pneumology and Thoracic Surgery,[7] it is considered to be positive when a fall of 20% occurs in FEV_1 with a methacholine concentration less than 8 mg/ml. The response can be classified as: slight (between 2 and 8), moderate (between 0.5 and 2), or serious (under 0.5). These are internationally agreed criteria.[13]

As only tests under 2 mg/ml are considered positive for ATUE purposes, a situation of inequality arises in the treatment of athletes who present a positive test with a PC20 of 2–8 mg/ml. If they were not athletes, they would be classed as having bronchial hyper-responsiveness and, according to the guidelines,[12] they could be treated with β_2 agonists. However, they are denied this possibility, and the number of athletes who may be affected by this situation is large: in our experience a third of the subjects studied! We can expect that this situation will be better in Torino 2006 with a positive level of 4 mg/ml. In fact, tables 1 and 2 show that four more athletes (three men and one woman) would be positive with this criterion.

Another aspect is that FEV_1 is used as the only criterion for positivity in the provocation tests in order to obtain an ATUE. In clinical practice, other flow variables can be considered as obstructive response indicators,[8] in particular the expiratory

What is already known on this topic

- Most regulations for doping control prohibit the use of β_2 agonist bronchodilators unless the subject follows the procedure known as abbreviated therapeutic use exemption (ATUE)
- This procedure requires proof of bronchial hyperresponsiveness at rest or after a provocation test with effort, eucapnic voluntary hyperpnoea test, inhalation of a hypertonic aerosol, or a methacholine test

What this study adds

- Although objective measures of airway function may be useful to prevent the non-indicated use of asthma drugs, it is necessary to be careful in establishing the indication as there are differences from the clinical criteria used for the general population; these differences affect the bronchodilation test and methacholine test
- It is not acceptable for bronchial obstruction criteria to be different if the patient is an athlete

flow between 25% and 75% of forced vital capacity and peak flow. We have found athletes who showed no fall in FEV_1 during provocation tests, but with significant changes in other flow variables measured on the flow volume curve.

These represent, in our opinion, a serious discrimination against asthmatic athletes as far as treatment is concerned. However, it could be justified if the use of inhaled β_2 agonists at therapeutic doses had clear ergogenic effects, but a review of the work carried out over the last 15 years seems to contradict such an hypothesis. In 1993, Fleck *et al*[14] studied 21 non-asthmatic cyclists divided into two groups. The experimental group was given 360 μg salbutamol before an effort test on a cycle ergometer, and the control group was given a placebo. The authors conclude that the administration of salbutamol did not have any effect on either performance or lung function even when the dose was twice that recommended. From 1994 to 1997 several double blind studies were reported comparing the effect of salbutamol and placebo after a maximum effort test[15–17] or a Wingate test.[18] None of them found significant differences in the variables related to aerobic performance, although one of them[19] found a difference favouring salbutamol in peak flow during recovery. Other authors[20–22] tried to determine if the use of high doses of β_2 agonists by healthy athletes improved their performance. They did not find any change in either lung function or the effort performance in comparison with those receiving placebo. So the inhalation of these drugs in high doses produces no effect on the performance of non-asthmatic athletes. Furthermore, Goubault *et al*[21] determined salbutamol in urine after inhalation of 800 μg of it and detected insignificant amounts, concluding that, for salbutamol to be detected in the urine, the doses must be very high or administered in other ways, such as orally or parenterally.

On the other hand, two studies reported that salbutamol may be an effective ergogenic aid in non-asthmatic people. In 2000, Van Baak *et al*[23] found an increase in the isokinetic force of quadriceps and ischiotibials in non-asthmatic men who took 4 mg salbutamol orally in comparison with those who took a placebo. Similar results were reported in 2005 by Caruso *et al*[24] who administered salbutamol orally in doses of 16 mg/day for 14 days.

CONCLUSIONS

In our opinion it is not justified that the bronchial obstruction criteria are different if the patient is an athlete, particularly as there is no evidence that inhaled β_2 agonists have ergogenic effects at therapeutic doses, although they may do if administered orally at doses very much higher than therapeutic ones. We are in favour of strict vigilance of fair play, but we believe that excessive control can lead to situations of inequality for asthmatic athletes. In the current situation, the physician who has to treat an asthmatic athlete is often denied the most effective therapeutic option. For all of these reasons we think that these aspects of the antidoping regulations must be reviewed. Measures could be adopted such as including a fall of 70% in FEV_1% as the indication for a bronchodilation test and extending the definition of a positive result for the methacholine test to a PC20 of 8 mg/ml.

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COMMENTARY

The authors put under the spotlight the critical decision, based on semiquantitative criteria, about the use of anti-asthmatic drugs in athletes. They point out the possible damage to asthmatic athletes because of the inadequate measurement of the major physiological variable (FEV_1) tested. In effect, normalisation of personal data together with a wider criterion (lowering the threshold) with regard to the doses of drugs used to show bronchial hyper-responsiveness would give the asthmatic athlete the chance of full breathing capacity without any extra benefit to performance. β_2 agonists at doses high enough to induce bronchodilation do not improve performance, particularly in endurance sports. Following the decisions of various international organisations (IOC, WADA, IAAF, FIFA, etc) about the use of drugs such as caffeine (with well known effects on performance), β_2 agonists should be allowed to be used at bronchodilating doses in more open conditions.

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ELECTRONIC PAGES

Online case reports

The following electronic only articles are published in conjunction with this issue of *BJSM* (See also page 312)

Sudden collapse of a young female cross country runner

A S Kashyap, K P Anand, S Kashyap

The case is reported of a young previously healthy female cross country runner who collapsed on completion of a cross country run. The cause of the collapse was non-cardiogenic pulmonary oedema as a manifestation of hyponatraemic encephalopathy. The concurrent occurrence of non-cardiogenic pulmonary oedema and encephalopathy due to hyponatraemia is unusual.

(*Br J Sports Med* 2006;**40**:e11) http://bjsm.bmjjournals.com/cgi/content/full/40/4/e11

Adolescent butterfly swimmer with bilateral subluxing sternoclavicular joints

P S Echlin, J E Michaelson

Sternoclavicular joint subluxation/dislocation injuries in the athlete are uncommon. They can be organised by degree (subluxation, dislocation), timing (acute, chronic, recurrent, congenital), direction (anterior, posterior), and cause (traumatic, atraumatic). The unusual case reported is an adolescent butterfly swimmer with recurrent bilateral sternoclavicular subluxation associated with pain and discomfort. The condition was treated and resolved with conservative management. The diagnosis, investigations, and treatment options are discussed.

(*Br J Sports Med* 2006;**40**:e12) http://bjsm.bmjjournals.com/cgi/content/full/40/4/e12